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IMMUNIZATION AGAINST TYPHUS FEVER.

A REPORT OF AN UNSUCCESSFUL ATTEMPT TO IMMUNIZE MONKEYS AGAINST TYPHUS INFECTION BY CULTURES OF B. TYPHI EXANTHEMATICI (PLOTZ)

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The following experiments were undertaken for the purpose of determining whether it is possible to immunize monkeys against typhus fever by means of a vaccine made from the *B. typhi exanthematici* (Plotz). While the results of the work throw light upon this point, any bearing they may have on the etiological relation of the organism to the disease is considered to be aside from the present discussion.

In the experiments to be reported, rhesus monkeys were injected subcutaneously at spaced intervals with living and dead cultures of *B. typhi exanthematici* (Plotz). After an interval of 12 days or more these animals and appropriate control monkeys received virulent typhus blood intraperitoneally.

The rectal temperatures of the monkeys receiving the vaccine were taken twice daily from the time of giving the first dose; that of the control monkeys from the time of receiving the test inoculation of virulent typhus blood. A rise of temperature occurring after an incubation period of about 10 days and lasting about 10 days was regarded as evidence of infection. We recognize that the indications of typhus infection in monkeys are not very striking, but controlled as the experiments were, by the inoculation of normal (nonvaccinated) monkeys and of immune monkeys, i. e., monkeys that had previously reacted to typhus, the results are regarded as trustworthy.

Procedure.

The cultures of *B. typhi exanthematici* (Plotz) were grown in glucose-broth fermentation tubes which had been heated and cooled just prior to inoculation. In this manner a good growth of the organism was obtained in the closed arm of the tube. Four days after inoculation an estimate of the number of organisms in the tubes was made and a dilution of the culture equivalent to 1,000,000,000 organisms was injected subcutaneously into each of six test monkeys. The vaccine represented four strains of the organism. In half of the tests the bacilli had been killed by heating to 60° C. for one hour before use; in the remainder live organisms were injected.

The virus of the virulent typhus blood used was that of Mexican typhus. The history of the strains used was as follows: The first was obtained on February 20, 1917, from a man 23 years of age, said to have been ill 11 days, who, for two days, presented an exanthem characteristic of typhus fever. The second strain was obtained on

March 13, 1917, from a man 22 years of age, in the fifth day of the fever, and in the third day of the exanthem. In both instances the patients were bled from the arm and the blood was diluted with an equal volume of physiological salt solution; about 6 cubic centimeters of the mixture were then injected into each of several guinea pigs. These were shipped to the Hygienic Laboratory and when the characteristic reaction to the typhus virus was observed the animals were bled from the heart, and other guinea pigs and monkeys were intraperitoneally inoculated with the blood. Thus two strains of the virus were available for experimental purposes.

The monkeys were injected with the vaccine on the first, eighth, and fifteenth day of the experiments. Not less than 12 days after the last of these injections of bacilli, the monkeys received from 3 to 4 cubic centimeters of virulent typhus blood intraperitoneally. At the same time for each vaccinated monkey one fresh monkey and one monkey which had previously reacted characteristically to the virus of typhus fever and was therefore considered to be immune, were inoculated in the same way with the same amount of the same sample of virulent typhus blood.

By consulting the protocols and charts it will be seen that in five of the six vaccinated monkeys the rise of temperature which is interpreted as evidence of typhus infection came somewhat later than in the nonvaccinated control monkeys. We are not prepared to express an opinion as to whether this is to be regarded as of significance.

With reference to the fresh monkeys, six in number, which were inoculated with typhus blood, it is to be noted that two of these animals failed to react satisfactorily to a single injection of the typhus blood. That this is not an uncommon occurrence is indicated by the experience of Anderson and Goldberger,[1] who noted that 22.5 per cent of the rhesus monkeys injected with typhus-fever blood failed to exhibit the characteristic febrile reaction, although some of them reacted to subsequent injections.

We consider it permissible to suggest that, as two of the six normal controls failed to react to the test inoculation of typhus blood, the dose given is not to be regarded as an overwhelming one.

Summary.

Neither the living nor the dead cultures of *B. typhi exanthematici* (Plotz) caused any observable disturbance of the temperature of the monkeys.

All the monkeys which had received *B. typhi exanthematici* (Plotz) exhibited temperature curves characteristic of the reaction to typhus fever in the monkey when given a test dose of typhus virus.

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[1] Hygienic Laboratory Bull. No. 86, p. 131.

Four of the fresh control monkeys showed typical reactions, while in one of the fresh animals the reaction was frankly negative and in one it was indefinite.

None of the typhus-immune animals, six in number, showed temperature reactions.

Conclusion.

Evidence has been presented that a bacterial vaccine prepared from *B. typhi exanthematici* (Plotz) failed to protect monkeys against typhus infection (Mexican).

Acknowledgment.

The strains of typhus virus used to produce the characteristic reaction for monkeys in the animals included in the experiments were obtained by Surg. Edward Francis, of the United States Public Health Service at Laredo, Tex., through the cooperation of Dr. E. Hernandez, of the Mexican Health Service, to both of whom we express our thanks.

PROTOCOLS.

The details of the experiment are set forth in the following protocols.

Experiment No. 1. (See Chart.)

On April 16, 1917, monkey No. X5, nine days after inoculation, exhibited a characteristic temperature reaction to typhus virus No. 2, which had been passed through one guinea pig and one monkey since the virus was obtained. It was accordingly bled from the heart, the blood being mixed with a little 5 per cent sodium citrate solution, and 3½ cubic centimeters of the blood were then injected intraperitoneally in each of the following animals:

A. Monkey No. T202. This animal had received subcutaneously 1,000,000,000 living *B. typhi exanthematici* (Plotz) on March 21, March 28, and April 4, 1917.

B. Monkey No. C1. A fresh monkey.

C. Monkey No. 1. A typhus-immune monkey which had reacted to virus No. 1 from March 20 to March 29, 1917.

RESULTS.

Monkey No. T202 developed a definite febrile reaction seven days after inoculation.

Monkey No. C1 developed an indefinite febrile reaction nine days after inoculation.

Monkey No. 1 developed no febrile reaction.

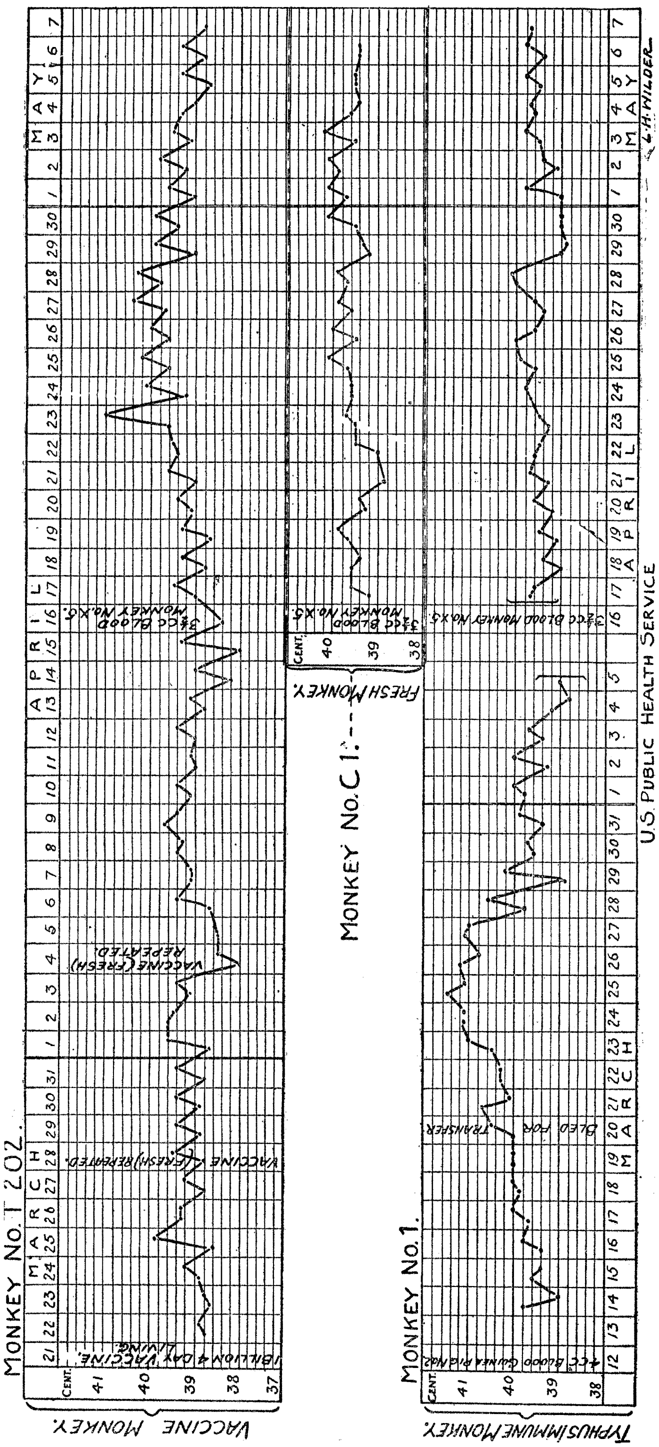
Experiment No. 2. (See Chart.)

On April 17, 1917, monkey No. X4, 10 days after inoculation, exhibited a characteristic reaction to typhus virus No. 2 which had been passed through one guinea pig and one monkey since the strain was obtained. It was accordingly bled from the heart, the blood being mixed with a little 5 per cent sodium citrate solution, and 3 cubic centimeters of the blood were then injected intraperitoneally into each of the following animals:

A. Monkey No. T204. This animal had received subcutaneously 1,000,000,000 living *B. typhi exanthematici* (Plotz) on March 21, March 28 and April 4, 1917.

B. Monkey No. T207. This animal had received subcutaneously 1,000,000,000 dead *B. typhi exanthematici* (Plotz) on March 21, March 28, and April 4, 1917.

C. Monkey No. C2X, a fresh monkey.



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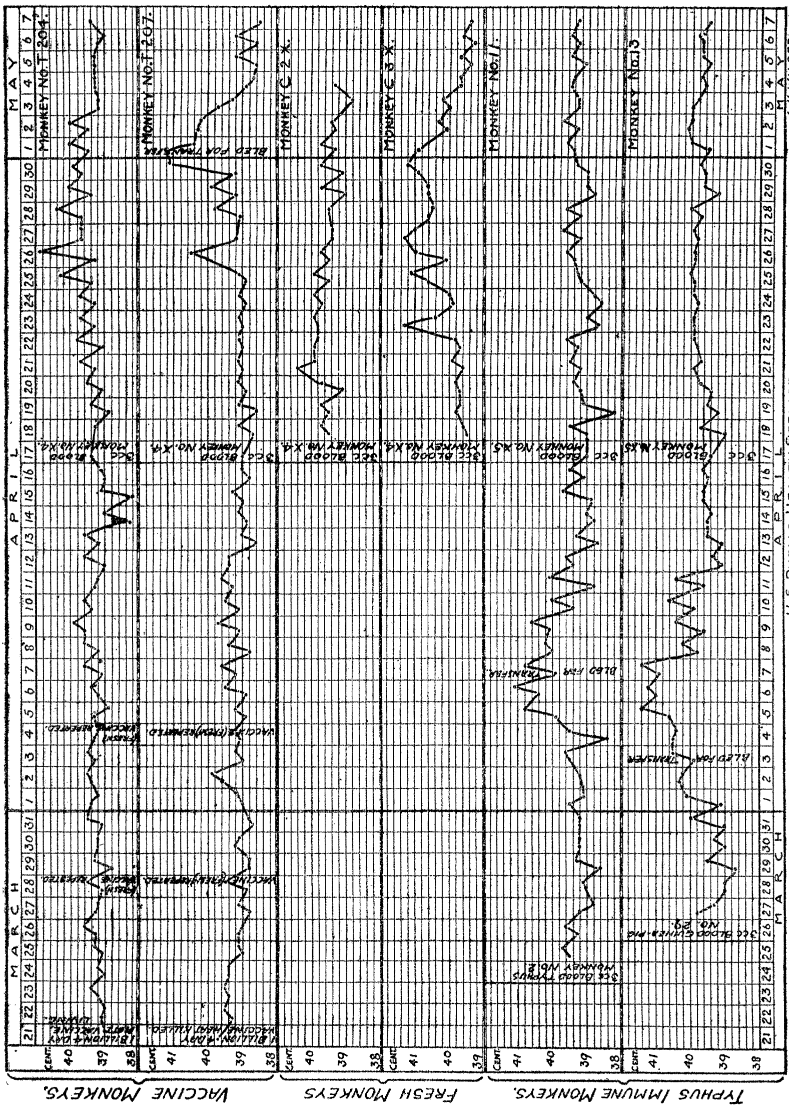
Experiment No. 1.

YOUR PATRIOTIC DUTY—BUY A 1917 LIBERTY BOND.



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D. Monkey No. C3X, a fresh monkey.

E. Monkey No. 11, a typhus-immune monkey, which had reacted to virus No. 1 from April 5 to April 11, 1917.

F. Monkey No. 13, a typhus-immune monkey, which had reacted to virus No. 1 from April 1 to April 11, 1917.

RESULTS.

Monkeys Nos. T204 and T207 developed definite febrile reactions eight and nine days, respectively, after inoculation.

Monkey No. C2X developed no febrile reaction suggestive of typhus.

Monkey No. C3X developed a definite febrile reaction six days after inoculation.

Monkeys Nos. 11 and 13 developed no febrile reactions.

Experiment No. 3. (See Chart.)

On April 27, 1917, monkey No. C3X, eight days after inoculation, exhibited a characteristic reaction to typhus virus No. 2, which had been passed through one guinea pig and two monkeys since the strain was obtained. It was accordingly bled from the heart, the blood being mixed with a little 5 per cent sodium citrate solution, and 4 cubic centimeters of the blood were then injected intraperitoneally into each of the following animals:

A. Monkey No. T208. This animal had received subcutaneously 1,000,000,000 heat-killed *B. typhi exanthematici* (Plotz) on March 21, March 28, and April 4, 1917.

B. Monkey No. C9X. A fresh monkey.

C. Monkey No. 2. A typhus-immune monkey which had reacted to virus No. 1 from March 22 to March 27, 1917.

RESULTS.

Monkey No. T208 developed a definite febrile reaction 14 days after inoculation and expelled a macerated fetus 4 days subsequently.

Monkey No. C9X developed a definite febrile reaction 9 days after inoculation.

Monkey No. 2 developed no febrile reaction.

Experiment No. 4. (See Chart.)

On April 29, 1917, monkey No. 22, 10 days after inoculation, exhibited a characteristic reaction to typhus virus No. 1 which had been passed through four guinea pigs and three monkeys since it was obtained. It was accordingly bled from the heart, the blood being mixed with a little 5 per cent sodium citrate solution, and 4 cubic centimeters of the blood were then injected intraperitoneally into each of the following animals:

A. Monkey No. T201. This animal had received subcutaneously 1,000,000,000 living *B. typhi exanthematici* (Plotz) on March 21, March 28, and April 4, 1917.

B. Monkey No. T215. This animal had received subcutaneously 1,000,000,000 heat-killed *B. typhi exanthematici* (Plotz) on March 21, March 28, and April 4, 1917.

C. Monkey No. C10. A fresh monkey.

D. Monkey No. C11. A fresh monkey.

E. Monkey No. 7. A typhus-immune monkey which had reacted to virus No. 1 from March 27 to April 6, 1917.

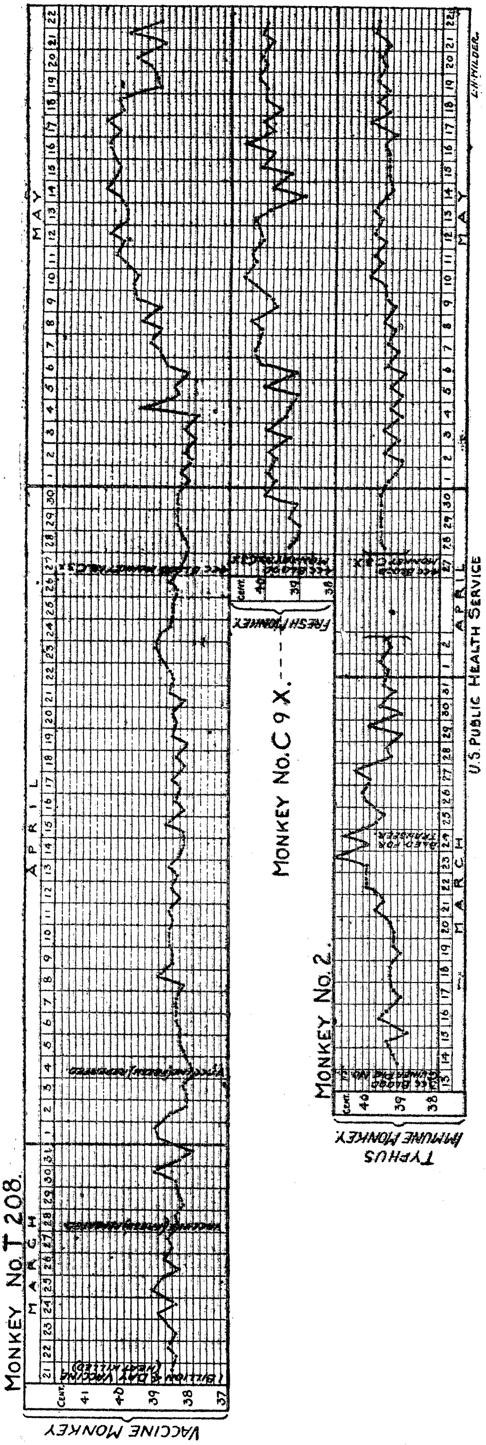
F. Monkey No. X4. A typhus-immune monkey which had reacted to virus No. 2 from April 16 to 23, 1917.

RESULTS.

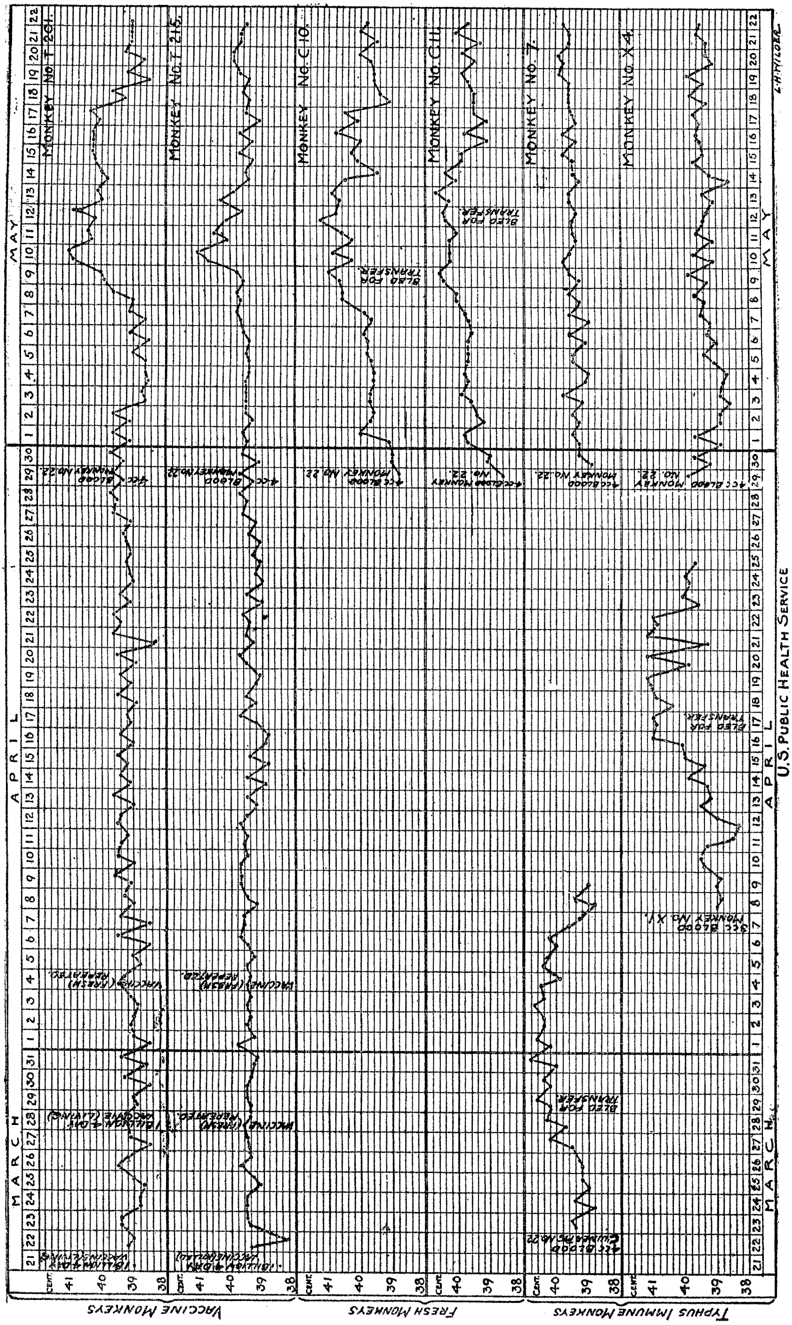
Monkeys Nos. T201 and T215 both developed definite febrile reactions 11 days after inoculation.

Monkeys Nos. C10 and C11 both developed definite febrile reactions 9 days after inoculation.

Monkeys Nos. 7 and X4 developed no febrile reactions.



Experiment No. 3.



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Experiment No. 4.